Table 2
Pre-Radiographic Lesions at the 12-Month Visit and 12-to-48 Month Incident TF Cartilage Damage (upper portion of table) and 12-to-48 Month Incident PF Cartilage Damage (lower portion of table). The table shows the frequency of knees with incident cartilage damage among knees without and with each lesion and the lesion present vs. absent adjusted odds ratio (OR) and associated 95% confidence interval (CI) for incident TF cartilage damage. Significant results are shown in bold italics. (TF = tibiofemoral; PF = patellofemoral)

	Number of knees without TF cartilage damage at the 12- month visit (457 knees from 457 persons with both knees K/L 0)	Number of knees (row%) with incident TF cartilage damage	OR (95% CI) adjusted for age, gender, BMI, previous knee injury, previous knee surgery, hand OA, physical activity
Bone marrow lesion, TF or PF or both *No bone marrow lesion (TF or PF)*	234	30 (12.8%)	1.83 (0.94, 3,57)*
	223	15 (6.7%)	*reference*
Bone marrow lesion, any TF *No TF bone marrow lesion*	64	8 (12.5%)	1.38 (0.60, 3.17)†
	393	37 (9.4%)	*reference*
Meniseal tear§,‖ *No meniscal tear*	56	6 (10.7%)	1.05 (0.39, 2.82)‡
	401	39 (9.7%)	*reference*
Meniscal extrusion§ *No meniscal extrusion*	37	6 (16.2%)	1.72 (0.63, 4.71)‡
	420	39 (9.3%)	*reference*
	Number of knees without PF cartilage damage at the 12- month visit (322 knees from 322 persons with both knees K/L 0)	Number of knees (row%) with incident PF cartilage damage	OR (95% CI) adjusted for age, gender, BMI, previous knee injury, previous knee surgery, hand OA, physical activity
Bone marrow lesion, TF or PF or both *No bone marrow lesion (TF or PF)*	94	18 (19.2%)	***2.68 (1.32, 543)***
	228	19 (8,3%)	*reference*
Bone marrow lesion, any PF *No PF bone marrow lesion*	52	14 (26.9%)	***4.26 (1.97, 9.22)***
	270	23 (8.5%)	*reference*

*hand OA also significant in this model, adjusted OR ***2.07 (1.02, 4.19)***.
†hand OA also significant in this model, adjusted OR ***2.09 (1.04, 4.20)***.
‡hand OA also significant in this mode), adjusted OR ***2.03 (1.004, 4.10)***.
§To adjust for the presence of the other meniscal lesion, meniscal tear and meniscal extrusion were included in the same model.
‖Of the 56 meniscal tears, 43 were horizontal tears, 8 were vertical, 1 was complex, and 4 menisci were partially macerated.

to determine extent of tissue pathology by MRI and evaluate its significance by testing the hypotheses: cartilage damage, bone marrow lesions, and meniscal damage are associated with incident persistent symptoms; bone marrow lesions and meniscal damage are associated with incident tibiofemoral cartilage damage; bone marrow lesions are associated with incident patellofemoral cartilage damage.
Methods: In a cohort study of 849 OAI (Osteoarthritis Initiative) participants who were Kellgren and Lawrence grade 0 in both knees, we assessed right knee (left if right technically inadequate) cartilage, bone marrow lesions, and meniscal damage on 12-month MRIs using MOAKS, as well as, in those at risk for each outcome, incident persistent symptoms (frequent knee symptoms or medication use for knee symptoms most days of a month in the past 12 months, at 2 consecutive annual OAI visits) by 5-year follow-up, and incident tibiofemoral cartilage damage and incident patellofemoral cartilage damage by 4-year follow-up. Multiple logistic regression (one knee/person) was used to evaluate associations between MRI lesions and each of these outcomes, adjusting for age, gender, BMI, knee injury, and knee surgery, (and, in cartilage damage models, further adjusting for hand OA and physical activity).
Results: 76% had cartilage damage, 61% had bone marrow lesions, 21% meniscal tears, and 14% meniscal extrusion. As shown in Table 1, in 573 knees (from 573 persons) at risk, cartilage damage (isolated patellofemoral; tibiofemoral and patellofemoral), bone marrow lesions (any; isolated patellofemoral; tibiofemoral and patellofemoral), meniscal tears, and BMI were associated with incident persistent symptoms. As shown in Table 2, in 457 knees at risk, hand OA but no individual lesion type was associated with incident tibiofemoral cartilage damage, and, in 322 knees at risk, bone marrow lesions (any; any patellofemoral) with incident patellofemoral damage. Having more lesion types was associated with a greater risk of outcomes.
Conclusions: In persons at higher risk but without any evidence of radiographic knee OA, cartilage damage, bone marrow lesions, and meniscal tears were associated with the new development of persistent symptoms, and bone marrow lesions with the new development of patellofemoral cartilage damage. These findings suggest that these lesions are not incidental in persons at higher risk and may represent early disease and illness.

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PREVENTION OF KNEE OSTEOARTHRITIS IN OVERWEIGHT FEMALES; EFFECT ON PROGRESSION OF MRI FEATURES AND KNEE PAIN

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Purpose: The preventive effect of a diet & exercise program and of oral glucosamine sulphate on the primary outcome 'clinical and radiographic knee osteoarthritis (OA)' in the PROOF study was borderline significant. Is it unknown what the effect is on the more sensitive secondary outcome 'progression of OA-features on magnetic resonance imaging (MRI)' and if such outcome is related with incident chronic knee pain. The aim of this study is to evaluate the preventive effects of the PROOF study on progression of MRI OA-features and to evaluate the association between progression of MRI OA-features and incident chronic knee pain.
Methods: In a 2x2 factorial design, the effects of a diet and exercise program (DEP) versus no intervention (DEP control) and of double-blind glucosamine sulphate (GS) versus placebo on the progression of MRI OA-features, were evaluated over 2.5 years in a high-risk group of 407 middle-aged women with a BMI $\geq$ 27 kg/m 2 and without knee OA during initial screening (PROOF study, ISRCTN 2823086). MRIs were scored using the MRI Osteoarthritis Knee Score (MOAKS). Progression of MRI OA-features was defined as progression of bone marrow lesions, cartilage loss, osteophytes or meniscus pathology (extrusion and morphologic change). Intention To Treat (ITT) and Per Protocol (PP) analysis for those compliant to DEP were performed on knee level using adjusted Generalized Estimating Equations. The same statistical model was used for the analysis between progression of MRI OA-features and incident chronic knee pain, defined as pain in the last 12 months and on most days of the previous month. Due to a known interaction between the two interventions (DEP and GS) on the primary outcome, the 3

groups (DEP + GS, DEP + placebo, DEP control + GS) were compared separately with the DEP control + placebo group as reference group.
Results: 687 knees of 347 women with mean age 55.7 years (± 3.2 SD) and mean BMI 32.3kg/m2 (±4.2 SD) had baseline and follow-up MRI available for analysis. There was no selective drop-out and the women were equally distributed over the 4 groups. ITT analysis showed a significant preventive effect in the DEP + placebo group on overall progression of meniscus pathology (OR 0.61, 95% CI [0.38 - 0.99], p-value (p) 0.046). PP analysis showed a significant preventive effect in the DEP + placebo group on overall progression of meniscus pathology (OR 0.43, 95% CI [0.22 - 0.84], p 0.014) and on overall progression of bone marrow lesions (OR 0.26, 95% CI [0.08 - 0.88], p 0.030). The 2 other groups (DEP + GS and DEP control + GS) showed no significant effects on overall MRI OA-features. When differentiated according to location in the knee, all effects were seen in the medial meniscus or at the medial tibio-femoral compartment. (ITT: medial meniscus extrusion: OR 0.47, 95% CI [0.24 - 0.91], p 0.025; medial bone marrow lesion: OR 0.33, 95% CI [0.14 -0.77], p 0.011, PP: medial bone marrow lesion: OR 0.13, 95% CI [0.02 - 0.93], p 0.042). Evaluating the effects of the MRI OA-features on pain, 42 of 347 women (12%) met the definition of incident chronic knee pain in one or both knees (52 of 687 knees (6.7%)). Progression of bone marrow lesions was significant associated with incident chronic knee pain (OR 2.1, 95% CI [1.02 - 4.46]).
Conclusions: A diet and exercise program has preventive effects on progression of meniscus pathology and on bone marrow lesions seen on MRI. Progression of bone marrow lesions is associated with incident chronic knee pain.

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DOES MEDIAL PATELLOFEMORAL OSTEOARTHRITIS MATTER? THE RELATION OF MRI-DETECTED STRUCTURAL DAMAGE IN THE MEDIAL AND LATERAL PATELLOFEMORAL JOINT TO KNEE PAIN: THE MOST AND FRAMINGHAM OSTEOARTHRITIS STUDIES

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Purpose: Contrary to the expectations of biomechanical models, we previously demonstrated a high prevalence of MRI detected cartilage loss in the medial patellofemoral joint (PFJ), both in unselected populations of older adults, and in selected populations at high risk of knee OA. However, it is unclear whether medial PFJ cartilage damage, though highly prevalent in older adults, contributes to knee pain. Given that cartilage is aneural, pain is expected only when full-thickness cartilage loss and/or bone marrow lesions (BMLs) are present. We therefore examined the relationship of MRI-detected full-thickness cartilage loss and BMLs in the medial and lateral PFJ with the presence and severity of knee pain in two large cohorts of older adults.
Methods: The Multicenter OA (MOST) Study cohort consists of older adults that have or are at risk of knee OA. The Framingham OA (FOA) cohort is a sample of the general population of older adults, unselected for pain or OA, living in Framingham, MA. In both NIH-funded studies, MRIs were read for cartilage loss and BMLs using Whole Organ MRI Scores (WORMS). Full-thickness cartilage loss was identified by WORMS 2.5, 5, or 6, while any size BMLs were identified by WORMS >0. For each of these two types of structural damage, we identified the PFJ region(s) in which damage was present as: none, isolated medial, isolated lateral and mixed (both medial and lateral). Knees were assessed for the presence (any pain in the past 30 days) and severity (MOST only using visual analog scale (VAS); 0-100) of knee pain. Using separate logistic regression models, we determined the relation of full-thickness cartilage loss and BMLs in each PFJ region with prevalent knee pain. We then compared the differences in VAS pain severity among PFJ regions using quantile regression (VAS pain scores were not normally distributed). Analyses were adjusted for age, sex, BMI, and concurrent structural damage in the tibiofemoral joint (TFJ). We repeated these analyses using WORMS >1 for BMLs and removing knees with TFJ damage.
Results: 1138 and 949 knees (one knee per subject) from MOST and FOA, respectively, had MRIs read and knee pain assessments. In MOST, the mean (sd) age and BMI was 68.9 (7.5) and 29.3 (4.7), respectively; 63.8% female. In FOA, the mean (sd) age and BMI was 63.4 (8.8) and 28.6 (5.6); 57.2% female. The prevalence of knee pain was 55.4% in MOST and 36.4% in FOA. Compartment associations with knee pain were not consistent across the two studies, although mixed disease was significantly associated with pain with each definition of structural pathology. In MOST, full-thickness cartilage loss in the medial PFJ was less strongly associated with knee pain than was lateral PFJ structural damage, while neither compartment individually was associated with pain when involvement was defined by BMLs (Table 1). Furthermore, the results of the quantile regression demonstrated that knee pain severity scores were greatest among knees with isolated lateral PFJ structural damage across a range of pain severity quantiles (Table 2),

Table 1
Relative odds of knee pain in knees with MRI-detected structural damage in the medial and lateral patellofemoral joint

	Full-thickness cartilage loss [WORMS= 2.5, 5 or 6)		Bone Marrow Lesion (WORMS >0)	
MOST (n=1138)	n of painful knees/ N of knees (%)	Adjusted OR* (95%CI)	n of painful knees/ N of knees(%)	Adjusted OR** (95%CI)
None	362/691 (52.4)	Reference	210/421 (49.9)	Reference
Isolated Medial	97/196 (49.5)	0.7 (0.5-1.0)	139/255 (54.5)	1.1 (0.8-1.5)
Isolated Lateral	89/133 (66.9)	1.8 (1.2-2.8)	91/150 (60.7)	1.4 (0.9-2.0)
Mixed	82/118 (69.5)	1.7 (1.1-2.7)	190/312 (60.9)	1.4 (1.0-1.9)
FOA (n=949)				
None	229/699 (32.8)	Reference	171/573 (30.0)	Reference
Isolated Medial	54/128 (42.2)	1.2(0.8-1.8)	67/157 (42.7)	1.6 (1.1-2.3)
Isolated Lateral	24/49 (49.0)	1.6 (0.9-3.0)	24/61 (39.3)	1.3(0.8-2.3)
Mixed	38/73 (52.1)	1.8 (1.1-3.1)	83/158 (52.5)	2.2(1.5-3.2)

*Adjusted for age, sex, BMI, depressive symptoms and TFJ cartilage loss **Adjusted for TFJ BMLs instead of cartilage loss.

Table 2
Difference of knee pain severity scores in knees with MRI-detected structural damage in the medial and lateral patellofemoral joint in the MOST cohort

	Full-thickness cartilage loss* (WORMS 2.5, 5 or 6)			Bone Marrow Lesions** (WORMS >0)		
	40th Percentile#	50th Percentile#	60th Percentile#	40th Percentile#	50th Percentile#	6th Percentile#
None (Reference)	0	0	0	0	0	0
Isolated Medial	0 (-0.4-0.4)	-0.3 (-1.3-0.8)	-1.1 (-2.8-0.6)	0.1 (-0.6-0.9)	0.4 (-0.8-1.5)	1.1 (-0.8-2.9)
Isolated Lateral	4.0 (1.5-6.5)	5.3 (2.0-8.6)	5.8 (2.7-90)	3.3 (1.0-5.6)	3.2 (0.5-5.8)	6.6 (1.7-11.5)
Mixed	5.0 (2.9-7.1)	4.1 (1.2-6.9)	4.7 (0.6-8.8)	1.6 (0.4-2.9)	3.1 (1.2-4.9)	3.4 (1.4-5.4)

*Adjusted for age, sex, BMI, depressive symptoms and TFJ cartilage loss.
**Adjusted for TFJ BMLs instead of cartilage loss.
#Difference in VAS pain score (95% CI); **Note**: Quantile regression results are shown for the 40th, 50th, and 60th percentiles only as there were too few subjects/data points in the other percentile categories.